Attorney Docket No.: 44342.011800

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: HIRABAYASHI et al.

SERIAL NO.: 09/646,135 Group Art Unit: 1635

FILED: September 8, 2000 Examiner: Whiteman, Brian A.

FOR: REMEDIES FOR HEPATITIS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 223313-1450

Declaration of Dr. Junichi Yano Under 37 C.F.R. §1.132

I, Junichi Yano, declare as follows:

1. I am a co-inventor of U.S. Patent No. 5,298,614 ("Yano 1") and European Patent Application EPO 685 457 A1 ("Yano 2"). I am familiar with what each of these documents disclose.

2. I received a Ph.D. of pharmacology from the Osaka University in 1975. My specialty was Nucleic Acids Chemistry. I studied Functional Nucleic Acid Molecules at the Johns Hopkins University in the United States from 1975 to 1979. I studied Gene Manipulation and Molecular Biology at Yale University in the United States from 1982 to 1984. I have been employed by Nippon Shinyaku Co., Ltd. since 1979. I became a General Manager of the Molecular Biology Department in the Discovery Research Laboratories in 1994, and then a Director of the Discovery Research Laboratories in the Research and Development division as a Corporate Officer in 1999. I became a member of the Board of Directors in 2005, supervising the Research and Development Division.

My major fields are Nucleic Acids Chemistry, Genetic Engineering and Genomic Drug Discovery.

3. I have read and understand U.S. Patent Application 09/646,135 (" '135 application'").

4. I have read and understand the Office Action ("Office Action") dated March 14, 2006 concerning the '135 application. I make this declaration to address several comments the Examiner has made concerning Yano 1 and Yano 2.

5. At pages 3-4 of the Office Action, the Examiner states:

> However, at the time the invention was made YANO 1 teaches that poly I: poly C is a substance having interferon induction action and can be used for treating viral infections (abstract and column 3, lines 32-40) YANO 1 further teaches that the substance can be used as a pharmaceutical substance in humans (column 16). YANO 1 further teaches that when the chain length is limited to certain ranges, the resulting substance exhibit desired physiological activity with markedly less toxicity (column 4, lines 31-39). . . . YANO 1 further teaches that the dsRNA can be delivered to an individual using different routes of delivery, including subcutaneous, intramuscular, or intravenous (column 18, line 32-46).

With all due respect, I disagree with the Examiner.

6. At column 3, lines 32-40, my co-inventor, Dr. Tadaaki Ohgi and I state that poly I: poly C is a substance having a significant activity, such as interferon induction. This activity was already known in the art. At column 3, lines 43-45, however, we further note that poly I: poly C "exhibits unexpectedly strong toxicity".

7. At no point in Yano 1 do we ever state that poly I: poly C "can be used for treating viral infections". In fact, Yano 1 stands for the opposite.

8. At the time we made the invention described in Yano 1, it was common knowledge among skilled artisans that poly I: poly C could not be used as a medicine because of its high toxicity even though it could induce a sufficient level of interferon. It

was for this reason that my co-inventor and I began investigating derivatives of poly I: poly C.

9. For this reason, I respectfully disagree with the Examiner's statement that Yano 1 teaches poly I: poly C "can be used for treating viral infections".

10. I also disagree with the Examiner's statement that "Yano 1 further teaches that when the chain length is limited to certain ranges, the resulting substance exhibit desired physiological activity with markedly less toxicity", at least to the extent that the Examiner seeks to apply this statement to poly I: poly C. This statement cannot be applied to poly I: poly C. In fact, as Test Example 3, Table 1 at page 13 of the '135 application demonstrates, shortened poly I: poly C alone cannot induce sufficient interferon levels in vivo for treating hepatitis.

11. In conclusion, limiting poly I: poly C to shortened (e.g., 100-500 bp) compounds results in substances with unacceptably low physiological activity in vivo. If we thought poly I: poly C would work we would have used that compound instead of investing substantial time and effort making and testing derivatives.

12. Finally, with respect to the Examiner's contention that Yano 1 teaches different routes of delivery, that teaching, at column 18, lines 32-46 of Yano 1, relates to the derivatives only. A skilled artisan would not have administered poly I: poly C in such a manner because of its toxicity.

13. At page 5 of the Office Action, the Examiner states:

> However, at the time the invention was made, YANO 2 teaches using a complex (2-0-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglycerol and a phospholipid, e.g., lecithin) to administer double stranded RNA to an individual and that using the lipid reduces toxicity of the double stranded RNA and improves the uptake efficiency of the double stranded RNA into cells ('457, abstract and pages 2-11). YANO 2 teaches that the complex

can be delivered intravenously, intrarterially, locally, and rectally (page 16).

While the Examiner's statement is true, Yano 2 does not describe the specific combination of the cationic liposome of the present invention with poly I: poly C, let alone with 100-500 bp poly(I):poly(C). Yano 2 makes no mention of 100-500 bp poly(I):poly(C). In addition, because of the known toxicity problems with poly I: poly C or the weak interferon-inducing activity in vivo of shortened poly(I):poly(C), a skilled artisan would not have combined poly I: poly C with the cationic liposome for administration to humans.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity or enforceability of the present application or any patent issued thereon.

Junichi Yano

Sep. 8, 2006
Date